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(54) Title: REGULATION OF NITRIC OXIDE SYNTHASE ACTIVITY

(57) Abstract

This invention relates to the regulation of the activity of the enzyme nitric oxide synthase, and in particular to regulation of activity of endothelial nitric oxide synthase (eNOS) and neuronal nitric oxide synthase (nNOS and nNOSμ). According to a first aspect, the invention provides a method of identifying modulators of AMPK–mediated activation of eNOS, comprising the step of testing putative modulators for their ability to increase or decrease phosphorylation of eNOS depending on the calmodulin and calcium ion concentrations. In an alternative aspect, the invention provides a method of identifying modulators of AMPK–mediated inhibition of eNOS, comprising the step of testing a putative modulator for its ability to decrease or increase AMPK–mediated phosphorylation of eNOS in the presence of limiting calcium ions. Preferably specific phosphorylation of threonine 495 is assessed. According to a second aspect, the invention provides a method of identifying modulators that either promote or inhibit phosphorylation of nNOS and nNOSμ at Ser–1417. Compounds which activate the AMP–activated protein kinase are expected to be useful in the treatment of ischaemic heart disease by promoting both glucose and fatty acid metabolism, as well as by increasing NOS activity to improve nutrient and oxygen supply to the myocytes and to reduce mechanical activity. These compounds would also have utility in the treatment of pulmonary hypertension and in obstructive airways disease.